

IN THE UNITED STATES PATENT OFFICE

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In re application of: :  
ANTON STUETZ :  
Serial No. 233,559 :  
Filed: February 11, 1981 :  
For: PROPENYLAMINES, PROCESSES :  
FOR THEIR PRODUCTION, PHARMACEUTICAL :  
COMPOSITIONS CONTAINING THEM AND :  
THEIR USE AS PHARMACEUTICALS :  
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DECLARATION UNDER RULE 132

I, GÁBOR PETRÁNYI, declare and say that:

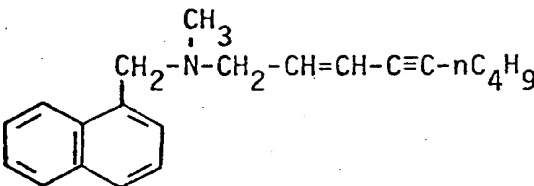
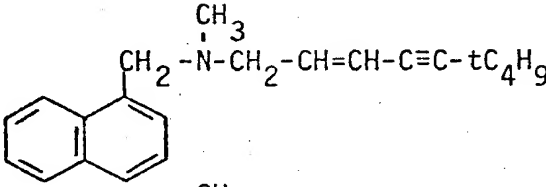
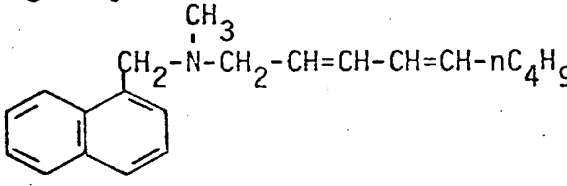
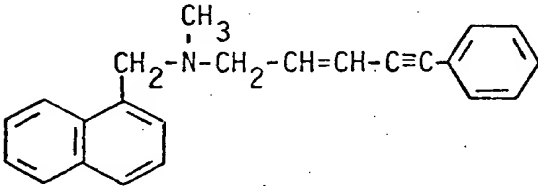
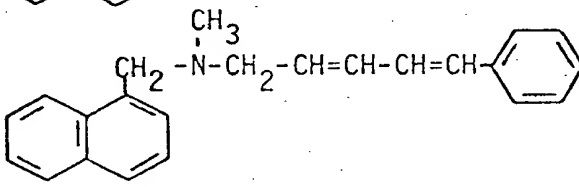
I am a German citizen residing at Bräuhausegasse 13, A-2320 Schwechat/Austria;

I obtained a doctorate of Veterinary Medicine from Justus Liebig-Universität, Giessen/Germany;

In 1969 I joined the Sandoz Research Institute, Vienne, where I have since been employed as a mycologist; and

that the following in vitro antimycotic test program was carried out under my supervision.

TEST COMPOUNDS

- A.  US Serno. 233,559  
Example 3
- B.  US Serno. 233,559  
Example 16
- (i)  EP Appln. No. 896  
Example 17
- C.  US Serno. 233,559  
Example 18
- (ii)  EP Appln. No. 896  
Example 16

(All compounds in "trans" form)

## TEST METHODS

The activities of the test compounds were determined by measuring their minimum inhibitory concentration (MIC) using the series dilution factor technique.

### DETAILS

#### Nutrient medium

1.8 ml Sabourand Dextrose 2% broth; pH = 6.5  
(Merck)

in test tubes. One tube per concentration/substance plus control.

#### Test strains

- a) Trichophyton mentagrophytes ~~var. quinekeanum~~  $\Delta$ 158
- b) Microsporum canis  $\Delta$ 150
- c) Epidermophyton floccosum  $\Delta$ 167
- d) Sporotrichum schenckii  $\Delta$ 177
- e) Aspergillus fumigatus  $\Delta$ 159
- f) Candida albicans  $\Delta$ 9
- g) Candida albicans  $\Delta$ 124
- h) Candida parapsilosis  $\Delta$ 39

All strains are inoculated in quantities of 0.1 ml, ( $10^3$  spores/ml: end-dilution) per tube.

#### Test substance

0.1 ml, per tube as solution or suspension in water, dimethylsulfoxide or N-methylpyrrolidone.

Concentration

<u>Strain</u>	<u>Concentration range</u>
a), b), c)	100-0.0015 $\mu\text{g/ml}$ (16 dilutions/factor 2)
d), e)	200-0,1 $\mu\text{g/ml}$ (11 dilutions/factor 2)
f), g), h)	200-0.05 $\mu\text{g/ml}$ (12 dilutions/factor 2)

Incubation

<u>Strain</u>	<u>Time</u>	<u>Environment</u>
a), b), c), d)	7 days	30°C 60% relative humidity
e)	72 hrs	" " " "
f), g), h)	48 hrs	" " " "

Evaluation

Following incubation the MIC is determined as the smallest amount of substance required ( $\mu\text{g/ml}$ ) in the nutrient medium to suppress growth when viewed by the naked eye.

## RESULTS

MHK - Values $\mu\text{g/ml}$	A	B	(i)	C	(ii)
Trichophyton mentagrophytes $\Delta 158$	0.02	0.006	0.05	0.4	1.56
Microsporum canis $\Delta 150$	0.02	0.006	0.1	0.8	12.5
Epidermophyton floccosum $\Delta 167$	0.05	0.006	0.1	0.8	12.5
Sporotrichum schenckii $\Delta 177$	0.8	0.4	1.56	>100	>100
Aspergillus fumigatus $\Delta 159$	25	1.56	25	>100	>100
Candida albicans $\Delta 9$	>100	6.25	>100	>100	>100
Candida albicans $\Delta 124$	>100	100	>100	>100	>100
Candida parapsilosis $\Delta 39$	0.8	0.1	6.25	>100	>100

## EVALUATION OF RESULTS

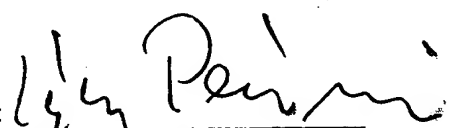
The compounds A, B and C exhibit unexpectedly and significantly superior anti-mycotic activity to the compounds (i) and (ii) respectively.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with that knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this

day of 12th September 1986

Declarant:

  
GÁBOR PETRÁNYI

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